

EDITORIAL COMMENT

Rate Control for Permanent Atrial Fibrillation

A Race (II) Worth Running?*

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A brief history of rate control for atrial fibrillation. The first attempt to control the ventricular rate in a patient with atrial fibrillation (AF) was likely the description by William Withering of a patient whose pulse became “more full and more regular” after the administration of digitalis leaf in 1785 (1). In the 1931 edition of “Diseases of the Heart,” Sir Thomas Lewis (2) wrote that the goal of rate control for patients with AF was to “reduce the ventricular rate to about 60 or 70 per min; the second object is to maintain the rate about 70 to 90 per min in circumstances of rest and light exercise.” There were obviously no studies at the time to support this directive. Seventy-five years later national guidelines recommended similar goals, still with no supporting evidence (3). Regardless, strict rate control of the ventricular response for patients with AF was accepted, because it made sense. Faster ventricular rates are often associated with more symptoms, produce deleterious hemodynamic status through a reduction in diastolic filling times, and can lead to tachycardia-mediated cardiomyopathy. For decades, these perceived insights fueled the wholesale adoption of strict rate control strategies, sometimes with deleterious effects.

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The first challenge to these widely held beliefs came from the results of 2 major rhythm versus rate control trials. Post hoc analyses of the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) and RACE (Rate Control versus Electrical cardioversion) studies showed no benefit of strict versus lenient rate control, although neither study was designed to specifically address this issue (4). This task fell to the RACE II (Rate Control Efficacy in permanent atrial fibrillation II) study, a randomized trial of

a lenient versus strict rate-control strategy that enrolled 314 patients with permanent AF of up to 12-month duration who were physically active, younger than 80 years of age, and had a resting heart rate above 80 beats/min (5). Goals for strict rate control were a resting heart rate of <80 beats/min and 110 beats/min during moderate exercise; lenient rate control goals were established at <110 beats/min at rest. Target heart rates were achieved in 98% of the lenient group but only 67% of the strict rate control group. As expected, the strict rate control group required a greater number of therapies at higher dose and more office visits to achieve target heart rate. During a follow-up period of up to 3 years, no significant differences were found in terms of the primary composite endpoint of major cardiovascular morbidity or mortality or secondary endpoints that included symptoms and functional status. On the basis of these findings, updated guidelines recommend a lenient rate control strategy for patients with permanent AF although this time supported by clinical trial data (6).

There were several issues in the original study that warrant emphasis, the most obvious being that one-third of those randomized to the strict rate control arm failed to achieve target heart rates. As a result, the difference in the mean resting heart rate between the strict and lenient rate control arms at study end might have been statistically different but were clinically quite similar to one another. Although a strategy of strict versus lenient rate control seemed to offer no benefits, the question still remained as to whether achieved rate control conferred a better outcome than lenient rate control. The exploratory analysis of the original RACE II cohort appearing in this issue of the *Journal* by Groenveld et al. (7) takes aim at this question and in doing so makes an important contribution to the care of the growing number of patients with permanent AF (8). **Strict rate control: attempt versus achievement.** The current analysis compares cardiovascular morbidity, mortality, and quality-of-life endpoints in those with lenient rate control with those that achieved and failed to achieve strict rate control at the end of the dose-adjustment phase in the original RACE II study. Nearly all of the patients originally randomized in the RACE II study were analyzed in the present study. Reasons for failed strict rate control included the absence of AF-related symptoms requiring tighter rate control, adverse events from the medical therapies, or inability to achieve target heart rate despite medical therapies. In the end, 608 of the original 614 RACE II cohort were included in the sub analysis, with 33% of those assigned to strict rate control now analyzed as the failed strict rate control cohort. At study end, the composite primary outcome was reached in 14.2% of those with successful strict rate control, 15.0% of those with failed strict rate control, and 12.1% of those with lenient rate control. Although the confidence intervals for the hazard ratios are wide, there is no suggestion from the data that those patients in whom strict rate control was achieved fared any

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better than those with lenient rate control or those in whom strict rate control could not be achieved. These results were consistent even among those patients with reduced ejection fraction at baseline, with the caveat that the number of patients in this group was small. Overall it can be argued that those with successful strict rate control actually did worse than their counterparts in the other 2 groups, because they required higher doses of more medications and needed more clinic visits to achieve the heart rate goals with no apparent clinical benefit.

Why is strict rate control no better than lenient rate control? It seems that the conclusions from the RACE II study might now be extended to those with attempted or achieved strict rate control, neither of whom seem to fare any better compared with those with a lenient rate control approach in terms of cardiovascular morbidity, mortality, or symptoms. Although a little rate control might in fact be good enough, some limitations remain. The original RACE II study found that, at the end of the follow-up period, the mean resting heart rate in the lenient-control group was 85 ± 14 beats/min compared with 76 ± 14 beats/min in the strict rate control group. In the present analysis, mean heart rates in those with achieved strict rate control or failed strict rate control, or randomized to lenient rate control were 75 ± 14 beats/min, 78 ± 12 beats/min, and 85 ± 13 beats/min, respectively. Even though the goal for lenient rate control was <110 beats/min, only 23% in the original cohort had heart rates >100 beats/min. In the end, it might be difficult to expect that differences in ventricular response of ≤ 10 beats/min could significantly impact the composite endpoint or improve symptoms in the permanent AF population, especially because most patients in the lenient rate control group were not even tachycardiac most of the time. More importantly, the number and doses of medical therapies needed to achieve strict rate control might offset any benefits of a modestly lower heart rate. Those patients in whom strict rate control was achieved were more likely to receive double or even triple atrioventricular nodal blocking agents, often at significantly higher doses. Whether these drugs alone or in combination contributed to increased event rates is purely speculative, although it is interesting to note that those who were assigned to but did not achieve strict rate control had numerically greater numbers of deaths from cardiovascular causes, cardiac arrhythmic death, cardiac non-arrhythmic death, congestive heart failure, need for pacemaker implantation, and death from any cause. One possibility is that these individuals experienced only the adverse effects of the prescribed agents but derived none of the benefits. Alternatively, one could hypothesize that some of those individuals that can be adequately rate controlled with fewer number and lower doses of medical therapies are inherently better off, perhaps as a result of intrinsic increases in parasympathetic tone.

Similar arguments might apply to the quality-of-life endpoints of the analysis. At baseline, more than one-half of the patients had symptoms including palpitations, dyspnea,

and fatigue with no significant difference between the 3 groups. By study end, all groups showed some overall improvement, particularly when it came to palpitations. Contrary to expectations, however, patients with successful strict rate control seemed to derive the least reduction in overall symptoms. Although it is possible that some complaints such as dyspnea and fatigue are unrelated to ventricular rate, one must also consider the possibility that once again the medical therapies required to achieve adequate rate control also create adverse symptoms that offset the salutary effects of slowed ventricular conduction. This concept is supported by the results of multiple “ablate and pace” studies, where strict rate control is achieved through atrioventricular nodal ablation without the use of medical therapies. Although these patients are invariably more symptomatic and have faster ventricular rates at baseline, this approach is almost universally associated with improvements in cardiac symptoms scores and quality-of-life measures (9).

Clinical implications of the RACE II study. In the wake of the AFFIRM, RACE, and RACE II studies, some might be tempted to take a nihilistic approach to AF therapies, because the evidence supporting a major morbidity or mortality benefit from rhythm control and now strict rate control strategies with medical therapies has been underwhelming. One unifying theme between the failure of rate and rhythm control strategies to show an improvement in these areas might lie in the limited efficacy of the available drug therapies and the adverse effects of the medications used to achieve the stated goals. Still, important lessons can be learned. First and foremost, there is little reason to do anything in medicine unless we can improve the duration or the quality of life. Strict rate control for permanent AF seems to do neither and therefore is not a race worth running. In contrast, a resting ventricular rate of <110 beats/min seems reasonable for most permanent AF patients in the absence of significant symptoms. Whether the same recommendation applies to patients with reduced ejection fraction is still uncertain, given the small proportion of enrollees with ejection fraction $<40\%$ and median follow-up times too short to allow tachycardia-mediated cardiomyopathy to manifest in some susceptible individuals (10). On a grander scale, the current analysis provides yet another example of how seemingly logical treatment strategies fail under the scrutiny of a rigorous clinical trial. Because it is estimated that only 1 in 9 American College of Cardiology/American Heart Association guideline recommendations are supported by the highest levels of evidence, this will certainly not be the last (11).

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